REMARKS

Overview

Claims 1-16, 19-27, and 29-33 are pending in this application. Claims 1, 2, 6, 19, 21, 24, and 30 have been amended. Claim 33 is new. Claims 23, 25-27 and 29 have been allowed. Claim 22 has been recognized as containing allowable subject matter but is objected to as depending from a rejected claim. Claims 1-16, 19-21, 24 and 30-32 have been rejected. Reconsideration is respectfully requested.

Issues under 35 U.S.C. § 112

Claims 2, 21, and 24 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner states that it is unclear whether claims 2 and 21 are intended to be an additional method step or a limitation of the constraints themselves. The Examiner also states that there is insufficient antecedent basis for the limitation in claim 24.

Claims 2 and 21 are intended to provide for an additional limitation to those defined constraints found in the parent claims. The Applicant has amended these claims to clarify the scope. In particular, claims 2 and 21 have both been amended to recite that "the logic constraints **are capable of protecting** against violation of a ...barrier." This language is the language suggested by the Examiner in the Advisory Action of July 11, 2006. Therefore, it is respectfully submitted that these rejections should be withdrawn.

Claim 24 has been amended to remedy the insufficient antecedent basis issue. Claim 24 provides further definition to the constraints of claim 23. Therefore, it is respectfully submitted that this issue has also been properly remedied.

Issues under 35 U.S.C. § 102

Claims 1-8, 10-12, 14-15, 19-21, and 30-31 have been rejected under 35 U.S.C. § 102(b) as being anticipated by HATZIMANIKATIS et al. (AIChE Journal (May 2006) Vol. 42, no. 5, pp. 1277-1229). These rejections are respectfully traversed.

Hatzimankikatis et al. discloses an approach to the analysis and synthesis of metabolic pathways. The problem of designating the regulatory structures built around a given metabolic reaction network is formulated as a MILP optimization problem. (p. 1289, first column, last paragraph). Hatzimankikatis et al. provides a mathematical description of metabolic reaction networks (p. 1279). Hatzimankikatis et al. provides a mathematical formulation of a synthesis problem as a MILP problem (p. 1281). Hatzimankikatis et al. allows for using constraints applied to the metabolic optimization problem (p. 1282).

Claim 1 requires "constructing a flux balance analysis model utilizing stoichiometric mass balances of metabolic and cellular composition information to identify boundaries for available flux distributions; applying logic constraints to the flux balance analysis model to thereby tighten the boundaries for the available flux distributions." Hatzimankikatis et al. does not disclose performing these steps. Referring to pp. 1282-83, Hatzimankikatis et al. describes applying constraints to its metabolic optimization problem. The constraints described by Hatzimankikatis et al. include mass balance for each metabolite; bounds on metabolites, manipulated variable rates, and metabolic outputs; constraints for the u_{mji} variables, and logical

9

constraints (pp. 1282-83). However, these constraints of Hatzimanikatis et al. are not logic constraints applied to the flux balance analysis model for tightening the boundaries for the available flux distributions. Therefore, this rejection to claim 1 should be withdrawn.

Claims 2-5, 20, and 21 depend from claim 1, therefore these rejections should be withdrawn for the reasons expressed with respect to claim 1. In addition, there is an independent basis for withdrawing this rejection from claim 2. Claim 2 requires "at least a subset of the logic constraints are capable of protecting against violation of a kinetic barrier." Hatzimanikatis et al. does not disclose that its logic constraints are capable of protecting against violation of a kinetic barrier. Note that Hazimanikatis discusses logical constraints at pp. 1282-83. Hatzimanikatis et al. disclose that "There are constraints based on the binary variables which are associated with the existence or nonexistence of various regulatory loops and the activation or deactivation of different continuously adjustable manipulated variables." Hatzimanikatis does not disclose these logical constraints are capable of protecting against a violation of a kinetic barrier. Therefore, this rejection to claim 2 should be withdrawn for this independent reason.

There is an independent reason for patentability of claim 3. Claim 3 requires "wherein the logic constraints further include a set of connectivity restraints. In Hatzimanikatis's discussion of logical constraints, there is no discussion regarding connectivity restraints. Therefore, this rejection to claim 3 should be withdrawn for this independent reason.

With respect to independent claim 6, claim 6 requires "constructing the flux balance analysis model utilizing stoichiometric mass balances of metabolic and cellular composition information to identify boundaries for available flux distributions; and applying a plurality of logic constraints to the flux balance analysis model to thereby tighten the boundaries for the available flux distributions." Hatzimanikatis does not disclose these limitations for the reasons

previously expressed with respect to claim 1. Therefore, this rejection to claim 6 should be withdrawn. As claims 7-8, and 10-15 depend from claim 6, it is respectfully submitted that these rejections should also be withdrawn.

There is an independent basis for the patentability of claim 8. Claim 8 requires "wherein the logic constraints are defined by a relationship between changes in reaction fluxes and metabolic concentrations." Understanding the relationship between changes in reaction fluxes and changes in metabolic concentrations provides a means by which to provide logic constraints based on qualitative information. Hatzimanikatis simply does not disclose this limitation. Therefore this rejection to claim must be withdrawn for this independent reason.

With respect to independent claim 19, claim 19 requires "a flux balance analysis model utilizing stoichiometric mass balances of the metabolic and cellular composition information to identify boundaries for available flux distributions; a plurality of logic constraints applied to the flux balance analysis model to tighten the boundaries for available flux distributions, the logic constraints selected from the set consisting of qualitative kinetic information constraints, qualitative regulatory information constraints, and differential DNA microarray experimental data constraints." It is respectfully submitted that this rejection should be withdrawn for the same reasons expressed with respect to claim 1.

With respect to independent claim 30, claim 30 requires "constructing the flux balance analysis model utilizing stoichiometric mass balances of metabolic and cellular composition information to identify boundaries for available flux distributions; applying a plurality of logic constraints to the flux balance analysis model to tighten the boundaries for available flux distributions; and applying mixed-integer linear programming to solve for a desired metabolic

outcome associated with the organism." It is respectfully submitted that this rejection should be withdrawn for the same reasons expressed with respect to claim 1.

Issues under 35 U.S.C. § 103

Claims 13, 16, and 32 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over HATZIMANIKATIS as applied to Claims 1-8, 10-12, 14-15, 19-21, and 30-31. In light of the amendment to independent claims 6 and 30, it is submitted that due to their dependencies, claims 13, 16, and 32 should also be allowed.

New Claim

Claim 33 is new. Support for claim 33 should be apparent from the original specification including at least original claims 1 and 8. Claim 33 is patentably distinguishable over Hatzimanikatis as claim 33 requires "determining logic constrains to apply to the flux balance analysis model to tighten the stoichiometric boundaries, the logic constraints based on qualitative relationships between changes in reaction fluxes and changes in metabolite concentrations; and applying the logic constraints to the flux balance analysis model to thereby tighten the stoichiometric boundaries." Hatzimanikatis does not, for example, disclose logic constraints based on qualitative relationships between changes in reaction fluxes and changes in metabolite concentrations.
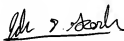
Conclusion

It is respectfully submitted that all pending claims are in proper form for immediate allowance. Reconsideration and passage to issuance are therefore respectfully requested. The

Examiner is invited to telephone the underlying attorney in order to reach mutual agreement as to claim limitation, should this amendment not place all claims in proper form for allowance.

This Amendment accompanies a Request for Continued Examination (RCE). Please charge Deposit Account No. 26-0084 the amount of $395.00 for the Request for Continued Examination (RCE). Please also charge Deposit Account No. 26-0084 the amount of $100.00 for one new independent claim over three. No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Respectfully submitted,

JOHN D. GOODHUE, Reg. No. 47,603
McKEE, VOORHEES & SEASE, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No: (515) 288-3667
Fax No: (515) 288-1338
CUSTOMER NO: 27407
Attorneys of Record

- pw/bjh -